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(FILE 'HOME' ENTERED AT 15:21:06 ON 17 JAN 2001)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, SCISEARCH, BIOTECHDS' ENTERED AT 15:21:13 ON 17 JAN 2001
L1 580117 S BINDING()SITE
L2 33 S L1 AND DRUG()MODEL?
L3 27 DUP REM L2 (6 DUPLICATES REMOVED)

=> d ibib abs l3 1

L3 ANSWER 1 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:41021 BIOSIS
DOCUMENT NUMBER: PREV200000041021
TITLE: Theoretical study of mexiletine and its interaction with cationic and anionic receptor sites.
AUTHOR(S): Remko, Milan (1); Smiesko, Martin; Benova, Adriana
CORPORATE SOURCE: (1) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Odbojarov 10, SK-832 32, Bratislava Slovenia
SOURCE: Farmaco (Lausanne), (Oct. 30, 1999) Vol. 54, No. 10, pp. 653-659.
ISSN: 0014-827X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Theoretical methods are applied to study the antiarrhythmic (AA) mexiletine (1-(2,6-dimethylphenoxy)-2-aminopropane). The AM1 method is used to construct a three-centre binding model for this drug. This model consists of an amine nitrogen atom that is protonated to a higher degree at physiological pH, flat hydrophobic regions of aromatic rings and additional functional groups with lone electron pairs of oxygen. Based on these ideas, a model for the binding of mexiletine at the transmembrane protein was constructed. An ab initio SCF method was used to study the two-component mexiletine-receptor **binding site** composed of acetate (Glu-, Asp-) and protonated methylamine (Lys+, Arg+). The binding of mexiletine to the receptor may be understood by considering a two-step process of recognition and binding of AA to its receptor. Within this model the mexiletine cation is recognised in the first step and bonded to the negatively-charged part of the receptor. In a subsequent step, the interaction between the amide oxygen and cationic amine group of the membrane protein may follow.

=> d ibib abs l3 2

L3 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:276786 CAPLUS
DOCUMENT NUMBER: 133:27761
TITLE: Polarized intercalation site in Z-DNA
AUTHOR(S): Taylor, Eric R.; Wiechelman, Karen
CORPORATE SOURCE: Department of Chemistry, University of Southwestern Louisiana, Lafayette, LA, 70504-4370, USA

SOURCE: Supramol. Chem. (1998), 9(1), 37-46
CODEN: SCHEER; ISSN: 1061-0278
PUBLISHER: Gordon & Breach Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Z-DNA can support an intercalation conformation exhibiting the 5'-pu-p-py-3' sequence specificity in contrast to the exptl. obsd. in B-DNA intercalation x-ray crystallog. DNA: **drug models**, however the **binding site** in Z-DNA is detd. by the alternating anti-syn backbone rather than base sequence. Z-DNA also exhibits a conformationally polarized intercalation site within the dimer repeat unit that is consistent with the neighbor exclusion principle. Addnl., Z-DNA conformers exhibit (pos.) winding of the dimer repeat unit upon assumption of the intercalation conformation.

REFERENCE COUNT: 62
REFERENCE(S):
(1) Arnott, S; Nature 1980, V287, P561 CAPLUS
(2) Arnott, S; Nature 1980, V283, P743 CAPLUS
(3) Berman, H; Proc Natl Acad Sci 1978, V75, P828 CAPLUS
(4) Berman, H; Stereodynamics of Macromolecular Systems 1979, P367 CAPLUS
(5) Bond, P; Proc Natl Acad Sci 1975, V72, P4825 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs l3 3

L3 ANSWER 3 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:255381 BIOSIS
DOCUMENT NUMBER: PREV199799554584
TITLE: Modeling, chemistry, and biology of the benzolactam analogues of indolactam V (ILV). 2. Identification of the **binding site** of the benzolactams in the CRD2 activator-binding domain of PKC-delta and discovery of an ILV analogue of improved isozyme selectivity.
AUTHOR(S): Kozikowski, Alan P. (1); Wang, Shaomeng; Ma, Dawei; Yao, Jiangchao; Ahmad, Shakeel; Glazer, Robert I.; Bogi, Krisztina; Acs, Peter; Modarres, Shayan; Lewin, Nancy E.; Blumberg, Peter M.
CORPORATE SOURCE: (1) Inst. Cognitive Computational Sci., Georgetown Univ. Med. Cent., 3970 Reservoir Road Northwest, Washington, DC 20007-2197 USA
SOURCE: Journal of Medicinal Chemistry, (1997) Vol. 40, No. 9, pp. 1316-1326.
ISSN: 0022-2623.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Protein kinase C (PKC) is a complex enzyme system comprised of at least 11 isozymes that serves to mediate numerous extracellular signals which generate lipid second messengers. The discovery of isozyme-selective activators and inhibitors (modulators) of PKC is crucial to ascertaining the role of the individual isozymes in physiological and pathophysiological processes and to manipulating their function. The discovery of such small molecule modulators of PKC is at present a largely unmet pharmacological need. Herein we detail our modeling studies which reveal how the natural product indolactam V (ILV) and its 8-membered ring analogue, the benzolactam 15, bind to the CRD2 activator domain of PKC. These modeling studies reveal that not all PKC ligands possess a common pharmacophore, and further suggest an important role of specific hydrophobic contacts in the PKC-ligand interaction. The modeling studies find strong experimental support from mutagenesis studies on PKC-alpha

that reveal the crucial role played by the residues proline 11, leucine 20, leucine 24, and glycine 27. Next, we describe the synthesis of two 8-substituted b[redacted]olactams starting from L-pheny[redacted]anine and characterize their isozyme selectivity; one of the two benzolactams exhibits improved isozyme selectivity relative to the n-octyl-ILV. Lastly, we report inhibition of cellular proliferation of two different breast carcinoma cell lines by the benzolactam 5 and show that the compound preferentially down-regulates PKC-beta in both cell lines.

=> d ibib abs l3 4

L3 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:657139 CAPLUS
DOCUMENT NUMBER: 126:54453
TITLE: Identification of a more potent analog of the naturally occurring alkaloid huperzine A. Predictive molecular modeling of its interaction with AChE
AUTHOR(S): Kozikowski, Alan P.; Campiani, Giuseppe; Sun, Li-Qiang; Wang, Shaomeng; Saxena, Ashima; Doctor, Bhupendra P.
CORPORATE SOURCE: Institute for Cognitive and Computational Sciences, Georgetown University, Washington, DC, 20007-2197, USA
SOURCE: J. Am. Chem. Soc. (1996), 118(46), 11357-11362
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Huperzine A (HA), a potent reversible inhibitor of acetylcholinesterase (AChE), is an important psychotherapeutic agent for improving cognitive function in Alzheimer's patients through the enhancement of central cholinergic tone. This mol. takes on added value in that it has recently been shown to exhibit neuroprotective properties (glutamate toxicity blocking activity) in vitro. Based upon our cumulative SAR information and to some extent the predicted **binding site** of HA within Torpedo AChE, we chose to investigate the synthesis and biol. of certain C-10 substituted analogs. The important finding was made that introduction of an axial Me group into the C-10 position of huperzine A increased the potency for AChE inhibition 8-fold; the corresponding equatorial isomer was about 1.5-fold less active than huperzine A. The introduction of substituents larger than Me resulted in a drop in activity. For example, the Et analog was found to be about 100-fold less active than huperzine A, indicating that while it is still capable of binding to Torpedo AChE, some steric interaction with the "walls" of the active site gorge must result. Through the use of mol. modeling methods involving the docking of these analogs to the reported X-ray crystal structure of Torpedo AChE, it is clearly evident that the C-10 axial Me group points into a hydrophobic region of the enzyme, while the equatorial Me group is directed to a less favorable hydrophilic region. Substituents larger than Me were found to result in a conformational energy penalty. The ready explanation of this structure-activity relationship data provides further evidence in support of our modeling studies aimed at establishing huperzine A's **binding site** in AChE. This knowledge should facilitate the identification of other structural analogs of huperzine A likely to exhibit an improved therapeutic profile.

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L3 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2

ACCESSION NUMBER: 1997:45724 CAPLUS
DOCUMENT NUMBER: 126:162030
TITLE: Carrier polymers for cisplat[redacted]-type anticancer **drug models**
AUTHOR(S): Neuse, Eberhard W.; Caldwell, Gregg; Perlwitz, Axel G.
CORPORATE SOURCE: Department Chemistry, University Witwatersrand, WITS, 2050, S. Afr.
SOURCE: Polym. Adv. Technol. (1996), 7(12), 867-872
CODEN: PADTE5; ISSN: 1042-7147
PUBLISHER: Wiley
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 21 refs. on the concept of polymer-drug conjugation and the use of platinum drugs in cancer therapy, the paper presents recent results in the synthesis of water-sol. polymeric carriers designed for the binding of antineoplastic coordination compds. of the cisplatin type. The target polymers, specifically, are linear aliph. polyamides comprising the ethylenediamine ligand system in the main chain as the potential metal **binding site**. With soly. in aq. media a key requirement for i.v. injectable conjugates, the polymers also contain hydrosolubilizing oligo(ethylene oxide) units in the chain, which serve the addnl. purpose of imparting resistance to serum protein binding and capture by the reticuloendothelial system. The synthesis methods include interfacial polymn., high-temp. soln. polycondensation in polyphosphoric acid and Michael addn. polymn., with 1,2-bis(2-aminoethylamino)ethane and 1,2-bis(3-aminopropylamino)ethane used as the amine comonomers providing the ethylenediamine ligand segment. The target polymers, crudely fractionated by dialysis in 25,000 mol.-mass cut-off tubing, are isolated by free-drying as water-sol. solids possessing.

=> d ibib abs l3 6

L3 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:820773 CAPLUS
DOCUMENT NUMBER: 123:218376
TITLE: Compounds interfering with periplasmic chaperone-pilus subunit interactions and pharmaceutical compositions for the treatment and prophylaxis of bacterial infections
INVENTOR(S): Hultgren, Scott; Kuehn, Meta; Xu, Zheng; Ogg, Derek; Harris, Mark; Lepisto, Matti; Jones, Charles Hal; Kihlberg, Jan
PATENT ASSIGNEE(S): Washington University, USA; Symbicon AB
SOURCE: PCT Int. Appl., 223 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9514028	A2	19950526	WO 1994-US13455	19941118
WO 9514028	A3	19950615		
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2176808	AA	19950526	CA 1994-2176808	19941118

AU 9511844	A1	19950606	AU 1995-11844	19941118
AU 704114	B2	19990415		
EP 730601	A1	19960911	EP 1995-90[redacted]3	19941118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09505309	T2	19970527	JP 1994-514666	19941118
US 6001823	A	19991214	US 1995-462436	19950605
US 6153396	A	20001128	US 1995-465275	19950605
PRIORITY APPLN. INFO.:			US 1993-154035	19931118
			WO 1994-US13455	19941118

OTHER SOURCE(S): MARPAT 123:218376

AB Novel methods for the treatment and/or prophylaxis of disease caused by tissue-adhering bacteria are disclosed. Compds. which bind to periplasmic mol. chaperones and prevent or inhibit the assembly of pili, and in vitro and in vivo methods for screening for such compds. as well as methods for the de novo design of these compds. are described. The latter method relies on novel computer **drug modeling** methods involving an approx. calcn. of binding free energy between macromols. Finally, novel pyranosides which are believed to be capable of interacting with periplasmic mol. chaperones are also disclosed. The cryst. structures of papD and a papG or a papK peptide was detd. and the interactions of papD with chaperone-derived peptides and of papD mutants with a papG peptide were studied. Two families of compds. which would bind to a papG **binding site** on papD were identified using the computer programs PLIM and PLIM-DBS (Symbicon AB). Several inhibitors of the hdo family (modeled on 6-hydroxydopamine) and several of the bpy family (modeled on (methyl-O,N,N-azoxyl)-methyl-.beta.-D-glucopyranoside) were synthesized. Assays to screen for compds. interfering with chaperone-pilus interactions were developed.

=> d ibib abs l3 7

L3 ANSWER 7 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER:	1995:210497 BIOSIS
DOCUMENT NUMBER:	PREV199598224797
TITLE:	Ring and Link Requirements for Tocainide Binding to the Class I Antiarrhythmic Drug Receptor on Rat cardiac myocytes.
AUTHOR(S):	Sheldon, Robert S. (1); Thakore, Ela
CORPORATE SOURCE:	(1) Calgary Gen. Hosp., 841 Centre Ave. E., Calgary, Alberta T2E 0A1 Canada
SOURCE:	Journal of Pharmacology and Experimental Therapeutics, (1995) Vol. 272, No. 3, pp. 1005-1010. ISSN: 0022-3565.
DOCUMENT TYPE:	Article
LANGUAGE:	English

AB Our purpose was to assess the structural and physicochemical determinants of the binding of tocainide and several of its homologs to the class I antiarrhythmic drug receptor associated with rat cardiac sodium channels. The homologs were chosen to assess the contributions of substituents of the aryl ring and the arylamine link on drug binding. Drug affinity was measured with a radioligand binding assay using (3H)Batrachotoxinin A 20-alpha-Benzoate and freshly isolated cardiac myocytes. The affinities of the homologs were compared to determine the relationship between the affinity for the receptor and the physicochemical and structural properties of the parent drug. The contributions to the free energy of binding were determined with the Gibb's equation DELTA-G = -RT In (1/K-i).

Hydrophobic interactions are important at most sites. Meta substituents on

the aryl ring and substituents on the link each interact hydrophobically with the receptor and contribute about 0.3 kcal/mol of carbon. The hydrophobic pocket near the link **binding site** accommodates at least six carbons. A para methoxy substituent reduces the free energy of tocainide binding by 43%. This profound reduction in the free energy of binding might be due to anomolously high aqueous solubility of alkyl aryl ethers. Longer alkoxy chains contribute 1.09 kcal/mol of carbon to the binding energy. Ortho substituents contribute little to binding specificity. These findings support a notion of a complex drug receptor with hydrophilic and hydrophobic domains that recognize specific moieties on class I antiarrhythmic drugs.

=> d ibib abs l3 8

L3 ANSWER 8 OF 27 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 94290813 MEDLINE
DOCUMENT NUMBER: 94290813
TITLE: Possible NMDA antagonist properties of drugs that affect high pressure neurological syndrome.
AUTHOR: Shuker M A; Bowser-Riley F; Davies S N
CORPORATE SOURCE: Department of Biomedical Sciences, Marischal College, University of Aberdeen.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1994 Mar) 111 (3) 951-5. Journal code: B00. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
AB 1. Previous studies have suggested that a series of **drugs modelled** on part of the strychnine molecule interfere with the development of high pressure neurological syndrome (HPNS) and it was presumed that this effect was via an action on inhibitory glycinergic transmission. We have now used the rat hippocampal slice preparation to examine the possibility that some of these drugs might instead have an action at the strychnine-insensitive (SI) glycine **binding site** associated with the NMDA receptor. 2. D-2-Amino-5-phosphonovalerate (AP5) and 7-chlorokynurenate (7CK) had no significant effect on the height of the population spike recorded from the CA1 region in 1 mM Mg2+ medium, but both blocked the multiple population spikes recorded in Mg(2+)-free medium. The effect of 7CK, but not AP5, was reversed by 200 microM D-serine which is consistent with the known antagonist action of 7CK at the SI-glycine site. 3. A derivative of benzimidazole, which shows the clearest structural similarities to known SI-glycine site antagonists and ameliorates HPNS, mirrored the effects of 7CK although it was considerably less potent. 4. Gramine, which exacerbates HPNS, significantly increased the number of population spikes evoked in Mg(2+)-free medium. 5. Mephenesin, which is the most potent known drug in ameliorating HPNS, had no significant effect on the response recorded in 1 mM Mg2+ and significantly reduced the number of population spikes recorded in Mg(2+)-free medium, but this effect was only partially reversed by the addition of D-serine. 6. The results are consistent with the benzimidazole derivative, but not gramine, being an antagonist at the SI-glycine receptor.(ABSTRACT TRUNCATED AT 250 WORDS)

=> d ibib abs l3 9

L3 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:2904 CAPLUS
DOCUMENT NUMBER: 120:2904

TITLE: Interaction of hydrophobic probes with serum albumin - influence of the side chain [redacted] d exciplex formation at the **binding site**

AUTHOR(S): Kumar, C. Vijaya; Tolosa, Leah M.

CORPORATE SOURCE: Dep. Chem., Univ. Connecticut, Storrs, CT, 06269-3060, USA

SOURCE: J. Phys. Chem. (1993), 97(51), 13914-19
CODEN: JPCHAX; ISSN: 0022-3654

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Novel fluorescent probes of the generic formula Ar-(CH2)n-NH3+ (Ar = 9-anthryl or 3-pyrenyl) were synthesized, and their binding properties with bovine serum albumin (BSA) have been evaluated. The anthryl probes 9-anthrylmethylamine hydrochloride (AMAC), N-Et (9-anthryl)methylamine hydrochloride (N-Et-AMAC), and 3-(9-anthryl)propylamine hydrochloride (APAC) showed small changes in their absorption spectra upon binding to BSA, whereas the pyrenyl analog, 4-(1-pyrenyl(butylamine hydrochliride (PBAC), showed a 5-nm red shift and an increase in the extinction coeff. at the peak positions. Such a red shift and increase in the intensity of the absorption transitions are consistent with binding of PBAC to hydrophobic sites on the protein. The fluorescence spectra of the anthryl and pyrenyl analogs exhibit different trends. The anthryl analog emission was quenched very effectively by increasing amts. of BSA (KSV .apprx. 2.6 .times. 103 M-1). In contrast, PBAC emission was quenched at low BSA concn. whereas at higher concns. of the protein the emission was enhanced. The fluorescence decays of the anthryl probes bound to the protein can be described by a short-lived and a long-lived component (10.6 and 6.7 ns for AMAC, 10.3 and 5.1 ns for APAC, 14.6 and 7.8 ns for N-Et-AMAC) indicative of at least 2 types of **binding sites**. In the case of PBAC, a third component was obsd. at probe:protein ratios higher than 1:5, which may be due to an exciplex formed at the **binding site**. Data from the equil. dialysis expts. indicate that the order of protein binding affinity of these probes is PBAC .mchgt. APAC > N-Et-AMAC > AMAC. Steady-state and time-resolved fluorescence quenching expts. with potassium iodide confirmed the above trend in the binding affinities. Upon binding to BSA, APAC and PBAC emission was extensively protected whereas only moderate protection has been obsd. for N-Et-AMAC and AMAC. A comparison of the binding properties of AMAC and N-ET-AMAC shows that increased distance of sepn. between the hydrophobic moiety and the cationic function enhances the protein binding affinity. Addnl., comparison of APAC with PBAC revealed the strong role of hydrophobic groups in the binding interactions. Therefore, the protein binding affinity of these probes depends on the degree of hydrophobicity of the arom. moiety and on the length of the linker sepg. the hydrophobic group from the cationic function.

=> d ibib abs l3 10

L3 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:260313 CAPLUS

DOCUMENT NUMBER: 120:260313

TITLE: Why are **binding-site** models more complicated than molecules?

AUTHOR(S): Crippen, G. M.; Bradley, M. P.; Richardson, W. W.

CORPORATE SOURCE: Coll. Pharm., Univ. Michigan, Ann Arbor, MI, 48109, USA

SOURCE: Perspect. Drug Discovery Des. (1993), 1(2), 321-8

CODEN: PDDDEC
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review discussion with 12 refs. A commonly occurring problem in drug development is that the binding affinities for a few compds. to a particular **binding site** on some protein have been measured, but the crystal structure for that protein is not available. Quant. structure-activity methods attempt to empirically correlate the binding data with various features of the chem. structures of the drug mols., so that one can predict the binding of novel compds. and thus aid the search for improved drugs. A common feature of nearly all these methods, however, is that they rely-implicitly or explicitly-on a guess as to the positioning of each mol. when bound to the common site. If one instead assumes that each mol. is free to seek out its optimal positioning in the site, then correlating the obsd. activity to mol. structure becomes more difficult, and can lead to surprisingly complicated site models. Here the authors show with some extremely simple artificial examples how this complexity necessarily arises.

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L3 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:569504 CAPLUS
DOCUMENT NUMBER: 121:169504
TITLE: **Binding site** models
AUTHOR(S): Hoeltje, Hans-Dieter; Anzali, Sohaila; Dall, Norbert; Hoeltje, Monika
CORPORATE SOURCE: Institute of Pharmacy, Free University of Berlin, Berlin, D-14195/45, Germany
SOURCE: 3D QSAR Drug Des. (1993), 320-35. Editor(s): Kubinyi, Hugo. ESCOM: Leiden, Neth.
CODEN: 60LYAZ
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 40 refs. Receptor mapping by model interaction calcns., calcium channel modulators, etc., are discussed.

L3 ANSWER 12 OF 27 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 92:463095 SCISEARCH
THE GENUINE ARTICLE: JG025
TITLE: ANIMAL AND **DRUG MODELING** FOR ALZHEIMER SYNAPTIC PATHOLOGY
AUTHOR: FRANCIS P T (Reprint); PANGALOS M N; BOWEN D M
CORPORATE SOURCE: INST NEUROL, MIRIAM MARKS DEPT NEUROCHEM, 1 WAKEFIELD ST, LONDON WC1N 1PJ, ENGLAND (Reprint)
COUNTRY OF AUTHOR: ENGLAND
SOURCE: PROGRESS IN NEUROBIOLOGY, (NOV 1992) Vol. 39, No. 5, pp. 517-545.
ISSN: 0301-0082.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 211

L3 ANSWER 13 OF 27 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 89:637739 SCISEARCH
THE GENUINE ARTICLE: CD141
TITLE: AN INVESTIGATION USING MOLECULAR MODELING OF CLASS-1A AND CLASS-1B ANTIARRHYTHMIC **DRUGS - MODELS** FOR THE DIFFERENTIATION OF **BINDING-SITES**

AUTHOR: MARRER S (Reprint)
CORPORATE SOURCE: FREE UNIV BERLIN, INST PHARMAZEUT, KONIGIN LUISE STR 2&4, 1000 BERLIN 33, FED REP GER (Reprint)
COUNTRY OF AUTHOR: GERMANY
SOURCE: PHARMACEUTICA ACTA HELVETIAE, (1989) Vol. 64, No. 12, pp. 338-344.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: German
REFERENCE COUNT: 22

L3 ANSWER 14 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1988:334907 BIOSIS
DOCUMENT NUMBER: BA86:41458
TITLE: EFFECT OF OLFACTORY BULBECTOMY AND CHRONIC AMITRIPTYLINE TREATMENT IN RATS TRITIATED IMIPRAMINE BINDING AND BEHAVIORAL ANALYSIS BY SWIMMING AND OPEN FIELD TESTS.
AUTHOR(S): STOCKERT M; SERRA J; DE ROBERTIS E
CORPORATE SOURCE: INSTITUTO DE BIOLOGIA CELULAR, FACULTAD DE MEDICINA, PARAGUAY 2155 2-P, 1121 BUENOS AIRES, ARGENTINA.
SOURCE: PHARMACOL BIOCHEM BEHAV, (1988) 29 (4), 681-686.
CODEN: PBBHAU. ISSN: 0091-3057.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB An 'animal model' of depression, based on bulbectomy, followed by chronic treatment with amitryptiline was used in rats. In the synaptosomal membranes of the cerebral cortex plus hippocampus, the number of **binding sites** for 3H-imipramine increased significantly when bulbectomy was associated with the antidepressant. In the bulbectomized rats the tendency was toward a decrease in binding. The treatment with 0.2% Triton X-100 of the membranes revealed a large increase in postsynaptic sites in the bulbectomized treated rats. The behavioral parameters analyzed by the swimming with a water wheel and the open field test revealed a series of differences in the various groups of rats, with respect to handling, bulbectomy and antidepressant treatment. Handling resulted in an increase in swimming time in controls, while bulbectomy reduced this parameter. In both the swimming and open fields tests, chronic bulbectomy reduces the motility of the rat. In control rats chronic amitryptiline increases locomotion and exploratory activity, a behavioral effect that is even more prominent in bulbectomized treated rats.

L3 ANSWER 15 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1988:463750 BIOSIS
DOCUMENT NUMBER: BA86:105469
TITLE: KINETIC EVIDENCE FOR A COMMON **BINDING SITE** FOR SUBSTRATES AND INHIBITORS OF THE NEURONAL NORADRENALINE CARRIER.
AUTHOR(S): SCHOEMIG E; KORBER M; BOENISCH H
CORPORATE SOURCE: INSTITUT FUER PHARMAKOLOGIE UND TOXIKOLOGIE DER UNIVERSITAET WUERZBURG, VERSBACHER STRASSE 9, D-8700 WUERZBURG, FRG.
SOURCE: NAUNYN-SCHMIEDEBERG'S ARCH PHARMACOL, (1988) 337 (6), 626-632.
CODEN: NSAPCC. ISSN: 0028-1298.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The neuronal noradrenaline uptake mechanism (uptake1) has been further characterized. For a number of substrates of uptake1 the half-saturating concentration (Km) and the maximal initial transport rate (Vmax) were determined. Furthermore, the dissociation constants (KD) for binding of these substrates to the desipramine **binding site** of the neuronal noradrenaline carrier were measured. The uptake experiments were done on rat phaeochromocytoma cells (PC12 cells), the binding experiments on purified plasma membranes of PC12 cells. The substrates

differed markedly in respect of Vmax, Km, and KD. Neither Km and Vmax nor KD and Vmax were found to be correlated. However, the discrepancy between Km and KD expressed as the ratio, Km/KD, was negatively correlated with Vmax ($r = -0.9315$, $n = 7$, $p < 0.01$). For the interpretation of these results a model on the basis of the steady-state assumption has been proposed for uptake1. From the mathematics of that model the following conclusions can be drawn. (1) The half-saturating substrate concentration(Km) is not identical with the dissociation constant for the binding of a substrate to the substrate recognition site (KD). (2) The discrepancy between Km and KD is expected to be negatively correlated with the maximal initial transport rate of the substrate (Vmax). The experimental results are in good agreement with the proposed model for uptake1. Especially the negative correlation between Km/KD and Vmax supports the hypothesis that desipramine inhibits uptake1 via binding to the substrate recognition of the neuronal noradrenaline carrier.

L3 ANSWER 16 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1988:28039 BIOSIS
DOCUMENT NUMBER: BA85:15764
TITLE: INFLUENCE OF COPPER IONS ON QUINACRINE HYDROCHLORIDE PHOTODYNAMIC ACTIVITY AND ITS INTERACTION WITH DNA.
AUTHOR(S): BLAGOI YU P; CHAIKINA L A; SHINDELKOVA E
CORPORATE SOURCE: A.M. GORKI KHARK. STATE UNIV., KHARKOV, USSR.
SOURCE: BIOFIZIKA, (1987) 32 (3), 383-387.
CODEN: BIOFAI. ISSN: 0006-3029.
FILE SEGMENT: BA; OLD
LANGUAGE: Russian
AB The influence of copper ions on the interaction between the antimalarial drug quinacrine (QA) and DNA is studied by polarized laser luminescence spectroscopy and fluorescence microscopy at molecular and cellular levels.
An alteration of quinacrine luminescence intensity in complex with DNA caused by copper ions is explained in terms of redistribution of QA molecules from quenching GC- to fluorescent AT-DNA **binding sites** due to the competition of Cu2+ with the dye. Mechanisms of component interactions in the triplex "DNA-QA-Cu2+ in model and cellular systems are shown to be in qualitative agreement. QA photodynamic activity change caused by Cu2+ action is explained on the basis of the ideas being developed.

L3 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:432581 CAPLUS
DOCUMENT NUMBER: 109:32581
TITLE: Analysis of data for [3H] quinuclidinyl benzilate binding to muscarinic cholinergic receptor sites in rat brain
AUTHOR(S): Yang, David
CORPORATE SOURCE: Ann Arbor, MI, 48105, USA
SOURCE: T'ai-wan Yao Hsueh Tsa Chih (1987), 39(2), 77-83
CODEN: JTPHAO; ISSN: 0368-4520
DOCUMENT TYPE: Journal
LANGUAGE: English
AB High-affinity **binding sites** and specificity for [3H]quinuclidinyl benzilate (QNB) were present in homogenates of rat cerebral cortex. The affinity of atropine was detd. for the muscarinic cholinergic receptor. The affinity const. was 0.094 nM and the apparent max. no. of binding sits was 1156.16 fmol/mg protein. Muscarinic antagonist, atropine, displace specific [3H]QNB binding with inhibition const. value equals to 0.47 nM and 50% ID equal to 2 nM. The Hill coeff. of atropine equals 1, which indicates that atropine has a reversible competition binding effect. Thus, atropine can serve as a **drug model** in demonstrating of [3H]QNB binding to muscarinic receptor sites in rat brain.

L3 ANSWER 18 OF 27 MEDLINE
ACCESSION NUMBER: 84176405 MEDLINE
DOCUMENT NUMBER: 84176405
TITLE: Interaction of hemoglobin S with anionic polysaccharides.
AUTHOR: Winter W P; Seale W R; Yodh J
CONTRACT NUMBER: HL-15160 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PEDIATRIC HEMATOLOGY/ONCOLOGY, (1984 Spring) 6 (1) 77-81.
Journal code: 35P. ISSN: 0192-8562.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198407
AB Our previous studies on the mechanism by which citrate agar electrophoresis separates hemoglobins led to the conclusion that hemoglobins bind to at least some sulfated polysaccharides. In the present report, we describe our deduction at the location of the **binding site** on the hemoglobin molecule. This led to the prediction, on theoretical grounds, that the anionic polysaccharides should possess anti-gelling actions toward hemoglobins and might be useful **drug models**. We have shown that anionic polysaccharides including heparin, lambda-carrageenan, dermatan sulfate, fucoidan, and agaropectin have anti-gelling activity. Evidence indicates that heparin can be introduced into red cells by synthetic lipid vesicles (liposomes) and that, once introduced, acts to block sickling. Because of the high solubility and low toxicity of the polysaccharides, we propose that these compounds deserve further study as potential anti-sickling agents.

L3 ANSWER 19 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1982:290967 BIOSIS
DOCUMENT NUMBER: BA74:63447
TITLE: TRITIUM LABELED CLONIDINE BINDING TO RAT HIPPOCAMPAL MEMBRANES.
AUTHOR(S): GEORGE C R
CORPORATE SOURCE: DEP. BIOL., N. C. CENTRAL UNIV., DURHAM, NC 27707.
SOURCE: NEUROCHEM RES, (1982) 7 (2), 205-212.
CODEN: NEREDZ. ISSN: 0364-3190.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Alpha adrenergic receptor subtypes in rat hippocampal membranes were studied, using [3H]clonidine as the radioactive ligand. On the basis of competitive binding studies, using the selective anatagonist-prazosin, WB-4101 and yohimbine, [3H] clonidine appeared to bind to a population of presynaptic sites that are pharmacologically similar to receptors previously classified as alpha2. A computerized model that linearized and produced the best possible fit to the experimental data points indicated that [3H]clonidine binds to a single population of receptors posessing equal affinity for the ligand. Binding data also indicated that rat hippocampus contains significantly fewer [3H]clonidine **binding sites** than rat cortex.

L3 ANSWER 20 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1981:282087 BIOSIS
DOCUMENT NUMBER: BA72:67071
TITLE: NONRANDOM OPENINGS AND CONCENTRATION DEPENDENT LIFETIMES OF
GLUTAMATE GATED CHANNELS IN MUSCLE MEMBRANE.
AUTHOR(S): GRATION K A F; LAMBERT J J; RAMSEY R; USHERWOOD P N R
CORPORATE SOURCE: DEP. ZOOL., NOTTINGHAM UNIV., UNIVERSITY PARK, NOTTINGHAM, NG7 2RD, UK.
SOURCE: NATURE (LOND), (1981) 291 (5814), 423-425.
CODEN: NATUAS. ISSN: 0028-0836.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Patch clamp studies of locust [Locusta migratoria] muscle were extended to
cover a range of glutamate concentrations and to include innervated muscle
and muscle not treated with concanavalin A [Con A]. The lifetime of the glutamate channel depends on the concentration of glutamate in the patch electrode, which is explained by a multi-**binding site** receptor model. This model, and the finding that channel openings occur non-randomly, accounts for the apparent transitions in channel lifetime described earlier.

L3 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:209372 CAPLUS
DOCUMENT NUMBER: 94:209372
TITLE: Interaction of 1-(2-tetrahydrofuryl)-5-fluorouracil with sodium poly-.alpha., L-glutamate
AUTHOR(S): Nishida, K.; Ando, Y.; Mochinaga, N.
CORPORATE SOURCE: Dep. Ind. Chem., Tokyo Univ. Agric. Technol., Koganei, 184, Japan
SOURCE: Colloid Polym. Sci. (1981), 259(3), 350-3
CODEN: CPMSB6; ISSN: 0303-402X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The binding of the anticancer drug 1-(2-tetrahydrofuryl)-5-fluorouracil (I) [17902-23-7] with the model protein Na polyglutamate [26247-79-0] was investigated. The .DELTA.G and .DELTA.H values for binding were .apprx.-10 kcal/mol and -11 kcal/mol, resp. The no. of **binding sites** decreased with increasing temp.: 574 (298K), 396 (308 K), 347 (318 K). The decrease was attributed to the bound I mols. acting as crosslinks at higher temps. The crosslinked polymer-I complex also had lower relative viscosity values compared to the random coil.

L3 ANSWER 22 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1982:211304 BIOSIS
DOCUMENT NUMBER: BA73:71288
TITLE: MEASUREMENT OF MEMBRANE POTENTIAL IN BACILLUS-SUBTILIS A COMPARISON OF LIPOPHILIC CATIONS RUBIDIUM ION AND A CYANINE DYE AS PROBES.
AUTHOR(S): ZARITSKY A; KIHARA M; MACNAB R M
CORPORATE SOURCE: DEP. MOLECULAR BIOPHYSICS AND BIOCHEMISTRY, YALE UNIV., NEW HAVEN, CONN. 06511.
SOURCE: J MEMBR BIOL, (1981) 63 (3), 215-232.
CODEN: JMBBBO. ISSN: 0022-2631.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Two of the commonly used probes for measuring membrane potential, lipophilic cations and the cyanine dye diS-C3 (5) [3,3'-dipropyl-2,2'-thiodicarbocyanine iodide], indicated nominally opposite results when tetraphenylarsonium ion was added as a drug to suspensions of metabolizing
B. subtilis cells. [3H]-Triphenylmethylphosphonium uptake was enhanced by the addition, indicating hyperpolarization, yet fluorescence of diS-C3 (5)
was also enhanced, indicating depolarization. Evidence is presented that both effects are artifactual and can occur without any change in membrane potential, as estimated by 86Rb+ uptake in the presence of valinomycin. The fluorescence studies suggest that tetraphenylarsonium ion displaces the cyanine dye from the cell envelope, or other **binding site**, into the aqueous phase. The uptake characteristics of the radiolabeled lipophilic cations were quite unusual. At low concentrations (e.g., < 10 .mu.M for triphenylmethylphosphonium) there was potential-dependent uptake of the label to a stable level but subsequent addition of nonradioactive lipophilic cation caused further uptake of

label to a new stable level. Labeled triphenylmethylphosphonium ion taken up to the 1st stable level could be displaced by 10 mM Mg2+; 86Rb+ uptake was unperturbed. Association of the lipophilic cations with the surface of deenergized cells was concentration-dependent, but there was no evidence for cooperative binding. This phenomenon of stimulated uptake in B. subtilis (which was not seen in Escherichia coli cells or vesicles) is consistent with a 2-compartment model with access to the 2nd compartment only being possible above a critical cation concentration. Such a model in which these 2 compartments are the cell surface and the cytoplasm, respectively, is tentatively proposed. Triphenylmethylphosphonium up to 0.5 mM exhibited linear binding to deenergized cells; binding of tetraphenylphosphonium and tetraphenylarsonium was nonlinear but was not saturated at the highest concentration tested (1 mM). The usual assumption, that association of the cation with cell surfaces is saturated and so can be estimated on deenergized cells, therefore leads to undercorrected estimates of cytoplasmic uptake in B. subtilis, and hence to overestimates of membrane potential. A more realistic procedure is described in which the estimate of extent of binding is based on a mean aqueous concentration related to the external concentration and to the much higher internal concentration that exists in energized cells. Using this procedure, the membrane potential in B. subtilis was estimated to be 120 mV, inside-negative. The procedure is of general applicability and should yield more accurate estimates of membrane potential in any system where there is significant potential-dependent binding.

L3 ANSWER 23 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1981:214963 BIOSIS
DOCUMENT NUMBER: BA71:84955
TITLE: INTERACTION OF PHLORIZIN AND SODIUM WITH THE RENAL BRUSH BORDER MEMBRANE D GLUCOSE TRANSPORTER STOICHIOMETRY AND ORDER OF BINDING.
AUTHOR(S): TURNER R J; SILVERMAN M
CORPORATE SOURCE: BUILD. 10, ROOM 6N320, NATL. INST. HEALTH, BETHESDA, MD. 20205.
SOURCE: J MEMBR BIOL, (1981) 58 (1), 43-56.
CODEN: JMBBBO. ISSN: 0022-2631.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The order and stoichiometry of the binding of phlorizin and Na to the [dog] renal brush-border membrane D-glucose transporter are studied. The experimental results are consistent with a random-binding scheme in which the ratio of phlorizin- to sodium-**binding sites** is 1 to 1. When the kinetics of phlorizin binding are measured as a function of increasing Na concentration, no significant variation is found in the apparent number of **binding sites**. The apparent **binding sites**. The apparent binding constant for phlorizin decreases rapidly from .apprx. 16 .mu.M at [Na] = 0 to 0.1 .mu.M [Na] = 100 mM and approaches 0.05 .mu.M as [Na] .fwdarw. .infin.. The experimental data are fit to a random carrier-type model of the coupled transport of Na and D-glucose. A complete parameterization of the phlorizin binding properties of this model under Na equilibrium conditions is given.

L3 ANSWER 24 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1980:269786 BIOSIS
DOCUMENT NUMBER: BA70:62282
TITLE: REDUCTION OF THE SYN ANTI GLYCOSYL CONFORMATIONAL BARRIER IN 2' DEOXY ADENOSINE UPON BINDING TO ETHIDIUM BROMIDE EVIDENCE FROM ULTRASONIC RELAXATION MEASUREMENTS.
AUTHOR(S): JORDAN F; NISHIKAWA S; HEMMES P

CORPORATE SOURCE: OLSON CHEM. LAB. RUTGERS, STATE UNIV., NEWARK, N.J. 07102, USA.

SOURCE: [redacted]AM CHEM SOC, (1980) 102 (11), 3[redacted]-3917.
CODEN: JACSAT. ISSN: 0002-7863.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB The unimolecular relaxation found by ultrasonic relaxation in dilute aqueous solutions of 2'-deoxyadenosine was examined in the absence and presence of ethidium bromide (a model for an intercalating drug) and indole-3-acetic acid at pH 7.0 (a model for tryptophan as a potential **binding site** on a protein). This relaxation, which was previously assigned to the syn-anti glycosyl isomerization, changes in terms of .intg.r and amplitude in the presence of the added reagents. Ethidium bromide and indole-3-acetic acid shift the relaxation frequency, .intg.r, to higher values. Detailed analysis of the data in the presence of varying amounts of ethidium bromide indicates that the apparent activation energy to syn-anti isomerization is decreased when 2'-deoxyadenosine is bound to ethidium bromide. 1H NMR studies were performed to elucidate the mechanism of binding. Assuming a 1:1 2'-deoxyadenosine-ethidium bromide (heterostack) complex, 1H NMR (in 2H2O) gives a Kheterostack of .apprx. 300 M-1 compared to the value derived from the ultrasonic data (in H2O) of .apprx. 400 M-1.

L3 ANSWER 25 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1979:69215 BIOSIS

DOCUMENT NUMBER: BR17:9215

TITLE: BEHAVIORAL AND BIOCHEMICAL PROPERTIES OF THE DOPAMINE RECEPTOR.

AUTHOR(S): CREESE I; SNYDER S H

SOURCE: LIPTON, MORRIS A., ALBERTO DIMASCIO AND KEITH F. KILLAM (ED.). PSYCHOPHARMACOLOGY: A GENERATION OF PROGRESS. XXVIII+1731P. ILLUS. RAVEN PRESS: NEW YORK, N.Y., USA, (1978) 377-388.
ISBN: 0-89004-191-1.

FILE SEGMENT: BR; OLD

LANGUAGE: Unavailable

L3 ANSWER 26 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1977:122017 BIOSIS

DOCUMENT NUMBER: BA63:16881

TITLE: LIGAND INTERACTIONS WITH THE ACETYL CHOLINE RECEPTOR FROM TORPEDO-CALIFORNICA EXTENSIONS OF THE ALLO STERIC MODEL FOR COOPERATIVITY TO HALF OF SITE ACTIVITY.

AUTHOR(S): GIBSON R E

SOURCE: BIOCHEMISTRY, (1976) 15 (17), 3890-3901.
CODEN: BICHAW. ISSN: 0006-2960.

FILE SEGMENT: BA; OLD

LANGUAGE: Unavailable

AB The solubilized acetylcholine (ACh) receptor from T. californica showed positive cooperativity in ACh binding with a dissociation constant of 1.2 .times. 10-8 M. Blockade of ACh binding by nicotine was competitive; blockade by d-tubocurarine appeared to result from an allosteric interaction that altered half of the ACh **binding sites** to a lower affinity form; decamethonium blockade displayed properties of competitive and allosteric inhibition suggesting less specificity for decamethonium binding than seen with either nicotine or d-tubocurarine inhibition data were evaluated by several possible models involving either differential competitive inhibition or allosteric inhibition. The data were best described by the allosteric model.

L3 ANSWER 27 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1975:161450 BIOSIS

DOCUMENT NUMBER: BA59:61450

TITLE: ELECTRON MICROSCOPIC MAPPING OF ADENINE THYMINE-RICH REGIONS AND OF ESCHERICHIA-COLI RNA POLYMERASE **BINDING SITES** ON THE CIRCULAR KINETOPLAST DNA OF TRYPANOSOMA-CRUZI.

AUTHOR(S): BRACK C; DELAIN E

SOURCE: J CELL SCI, (1975) 17 (2), 287-306.
CODEN: JNCSAI. ISSN: 0021-9533.

FILE SEGMENT: BA; OLD

LANGUAGE: Unavailable